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Original investigation

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The Association Between Treatment Adherence to Nicotine Patches and Smoking Cessation in Pregnancy: A Secondary Analysis of a Randomized Controlled Trial

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Abstract

Introduction: In nonpregnant "quitters," adherence to nicotine replacement therapy (NRT) increases smoking cessation. We investigated relationships between adherence to placebo or NRT patches and cessation in pregnancy, including an assessment of reverse causation and whether any adherence: cessation relationship is moderated when using nicotine or placebo patches.
Methods: Using data from 1050 pregnant trial participants, regression models investigated associations between maternal characteristics, adherence and smoking cessation.
Results: Adherence during the first month was associated with lower baseline cotinine concentrations (β –0.08, 95% confidence interval [CI] –0.15 to –0.01) and randomization to NRT (β 2.59, 95% CI 1.50 to 3.68). Adherence during both treatment months was associated with being randomized to NRT (β 0.51, 95% CI 0.29 to 0.72) and inversely associated with higher nicotine dependence. Adherence with either NRT or placebo was associated with cessation at 1 month (odds ratio [*OR*] 1.11, 95% CI 1.08 to 1.13) and delivery (*OR* 1.06, 95% CI 1.03 to 1.09), but no such association was observed in the subgroup where reverse causation was not possible. Amongst all women, greater adherence to nicotine patches was associated with increased cessation (*OR* 2.47, 95% CI 1.32 to 4.63) but greater adherence to placebo was not (*OR* 0.98, 95% CI: 0.44 to 2.18).
Conclusion: Women who were more adherent to NRT were more likely to achieve abstinence; more nicotine dependent women probably showed lower adherence to NRT because they relapsed to smoking more quickly. The interaction between nicotine-containing patches and adherence for cessation suggests that the association between adherence with nicotine patches and cessation may be partly causal.
Implications: This study used placebo randomized controlled trial data to investigate both associations between women's characteristics and adherence to NRT patch treatment, and the relationship between adherence to NRT patch treatment and odds of cessation in pregnant quitters. Greater adherence was seen with NRT patches, and greater adherence with NRT patches increased the odds of smoking cessation. A likely explanation for findings is that NRT patches, if used sufficiently, may

be effective for at least some pregnant women who try to stop smoking. Trials testing interventions which encourage women's adherence to higher dose NRT are indicated.

Introduction

Smoking in pregnancy is a substantial cause of ill health and the leading preventable cause of poor health outcomes for both mothers and babies.[1] Nicotine replacement therapy (NRT) is an effective medication for smoking cessation[2] but it is unclear whether it works in pregnancy.[3] A potential reason for the apparently lower efficacy of NRT in pregnancy is poor adherence to treatment; from randomized controlled trials included in a Cochrane review, only 7%–30% of pregnant women who received NRT reported finishing a complete course.[3] Adherence to NRT in nonpregnant smokers appears to be much higher.[4–7] The reasons for low adherence to NRT amongst pregnant smokers are not well researched but qualitative work suggests women's attitudes are at least partially responsible as some pregnant smokers have substantial concerns about potential fetal harms from nicotine.[8] However, as nicotine metabolism accelerates in pregnancy,[9,10] pregnant smokers may need higher nicotine doses to combat nicotine withdrawal, and high levels of treatment adherence may be particularly important for these women to achieve cessation.

In nonpregnant smokers, adherence to NRT is causally associated with smoking cessation[4–7]; prescribing more NRT patches is associated with greater use of NRT which in turn is positively associated with achieving cessation.[5] Additionally "reverse causation" or stopping NRT treatment because of relapse to smoking does not appear to explain the adherence-cessation association.[4–7] The significance of strong adherence to NRT by pregnant "quitters" is less well defined and to date has only been investigated in one study.[11] This study found that NRT used within 48 hours of quitting was associated with longer term use and also that women who used NRT for longer periods were more likely to be abstinent at 38 weeks gestation.[11] However, these analyses did not account for confounding factors, so should be interpreted with caution. We hypothesize that efficacy of NRT in pregnancy is dependent on high levels of treatment adherence and, in this paper, we use data from a large trial of NRT used in pregnancy (the SNAP trial)[12] to further investigate the relationship between adherence to NRT and smoking cessation amongst pregnant smokers. If our hypothesis is correct, one would expect to find a positive association between greater adherence to NRT and cessation that is not due to reverse causation (ie, that is not due to smokers that have lapsed to smoking not achieving cessation, as has been found in nonpregnant smokers).[7] In a series of analyses, therefore, we (1) investigate which characteristics of participants are associated with adherence to trial treatments; (2) determine the nature of any relationship between trial participants' adherence to treatment patches and the odds of smoking cessation, including the extent to which this might be explained by their characteristics; (3) investigate whether reverse causation explains the apparent adherence-cessation association; and (4) determine whether there is evidence of an interaction between adherence, type of patch used (ie, placebo or nicotine) and the odds of cessation.

Methods

Data Source, Baseline Variables and Provision of Trial Patches

Data collected during the SNAP trial[12] were used to investigate adherence to standard dose 15mg/16h NRT or placebo transdermal patches when used for smoking cessation in pregnancy. Prior to randomization, data were collected on: age, ethnicity, age full-time education completed, number of cigarettes smoked before pregnancy and currently, time after waking until first cigarette of the day, partners' smoking status, parity, gestational age, body mass index (BMI) and previous use of NRT in the current pregnancy. Saliva samples for cotinine estimation were also taken. Before randomization, participants were informed to stop using patches if they restarted smoking, because of the potential importance with regards to fetal health. After randomization, patches were issued in 4-week batches; women were asked to begin using them on their quit dates and, if they were abstinent at 1 month and wished to receive more, they then were given a second batch.

Adherence and Cessation Definitions

Adherence

At 1 month and delivery, participants were asked about their smoking behavior and the number of days on which they had used trial patches. At 1 month participants could report using patches for a maximum of 28 days and, at delivery for a maximum of 56 days; adherence was measured with respect to these values. Women for whom there were no adherence data were considered to have zero days' adherence.

Cessation

At 1 month, participants were asked about their smoking status in the last 24 hours and also since their quit date, which had been set shortly after randomization. If they reported abstinence from their quit date to 1 month postquit, this was validated using an exhaled carbon monoxide reading (<8 ppm). At delivery, participants who reported abstinence between their quit date and delivery had this validated using exhaled carbon monoxide measurement (<8 ppm) and/or saliva cotinine estimation (<10 ng/ml). Those who reported prolonged abstinence (ie, smoking no more than five cigarettes) from quit date to respective follow-up points and in whom this was validated, were considered to have achieved validated cessation.

Transformation of Adherence Data

Adherence data reported at 1 month was deemed to be sufficiently normally distributed that transformation was not needed; however, adherence data reported at delivery was square root transformed to adjust for the positive skew of the data (Skewness 1.80, Kurtosis: 6.62, where normal distributions have skewness and kurtosis of 0 and 3, respectively). The number of days that trial patches were used is a count measure and transformation of this meant that adherence, when used as an outcome, better fitted the assumptions of linear regression by assuming a more normal distribution.[13] The transformed variable was only used when adherence was an outcome variable, that is, in analyses investigating the relationship between maternal characteristics and adherence. The results of the regression findings were then back-transformed to allow clinically meaningful interpretations.

Analysis Strategies

Investigation of Relationship Between Women's Characteristics and Adherence to Trial Patches (Objective I)

Linear regression analyses were used to assess univariable associations between data describing participants' characteristics at

baseline and adherence reported at 1 month postquit date and also at delivery. All baseline variables were tested for collinearity; however, no associations were found. Then, the following model building strategy was performed to construct two multivariable parsimonious models using adherence data from 1 month and delivery as outcome variables. Firstly, all variables found in univariable analyses to be significant at a level of $P \leq .05$ were entered into a multivariable model and those subsequently found to be nonsignificant within this ($P > .05$) were then removed. Next, variables which had not been found to have significant univariable associations with adherence were added one at a time to the multivariable models to determine if they were now associated with adherence to treatment.

Investigation of the Relationship Between Adherence and Cessation and Whether Confounding Explains This (Objective II)

Multivariable logistic regression analyses were constructed for validated cessation at 1 month and delivery, using the same model building strategy as described above. Treatment assignment was included as an a priori confounder of this association, with the rationale being that an effect of adherence to treatment would only be expected in the group receiving nicotine patches. In addition, heaviness of smoking index (HSI) was also considered an a priori confounder as it is known to be a marker of addiction to tobacco.

Investigation of Reverse Causation as an Explanation for Adherence-Cessation Association (Objective III)

To investigate whether reverse causation may explain an apparent association between adherence and cessation, we conducted an analysis restricted to women who were assigned NRT patches and recorded as abstinent from smoking at 1 month following their quit date. In this group, any observed association between adherence and cessation could not be explained by reverse causation, as all women were still abstinent and restarting smoking would not explain their decision to stop using assigned NRT patches. This analysis used early adherence, whilst abstinent, as a proxy for later adherence and operated under the assumption that women with high early adherence would also have greater adherence after 1 month into the trial when their abstinence from smoking was measured for the first time and this later adherence would be causally associated with abstinence. Thus, a logistic regression analysis was used to compare the odds of cessation at delivery and adherence to NRT patches, ascertained using the median split in the number of days NRT patches were used within the first 28 days following their quit date.

Investigation of Whether or not a Treatment Assignment-Adherence Interaction Exists for Smoking Cessation (Objective IV)

Logistic regression analyses were performed to assess whether the interaction between NRT assignment and adherence to patches (using median split as defined above) was significantly associated with the odds of cessation at delivery. If high adherence to NRT patches was significantly associated with higher rates of abstinence than high adherence to placebo patches, this would demonstrate that NRT patches have a greater effect on cessation the more they are used. We performed a sensitivity analysis to assess the significance of the interaction test between adherence and treatment assignment on the odds of cessation as delivery in a subgroup of women who were validated as abstinent at 1 month, where reverse causation would not be possible.

Complete case analyses were conducted for all objectives. All analyses were conducted using Stata 13.1 (College Station, TX).

Results

Of 1050 women randomized in the SNAP trial,[12] analyses for objectives I, II and the first analysis to address objective IV, were conducted in 957 (91.1%) women who had no missing data for baseline characteristics. Analyses to address objective III and the second analysis addressing objective IV were conducted within the 167 (15.9%) women who were abstinent up until 1 month postquit date. Women who did not report the age they left full-time education all failed to achieve cessation, and so were excluded from the analysis (n = 14, 1.3%). We also excluded 80 women (7.6% nondisclosure rate) where there were no data on cotinine concentration at baseline. Adherence data were available for 865 women at 1 month and for 981 women at delivery. Missing data for adherence was imputed as zero days used for the women included in the analysis as it was likely that women who did not report adherence had lapsed to smoking and were not using patches; this imputation was made for 15.9% and 6.4% of participants at 1 month and delivery respectively. The baseline maternal characteristics of the main study group (N = 957) and the restricted study group (N = 167) are included in Table 1 and Table 2, respectively.

Adherence

Maternal age, level of education, ethnicity, primiparity and gestational age amongst low and high adherers were similar for women included in the complete case analyses (n = 957) for objectives I and II (Table 1). The baseline characteristics of the 167 women in the restricted group, which was used in the analyses for objectives III and IV, were similar to the 957 women analyzed in objectives I and II with respect to maternal age and gestation (Table 2). The following are adherence statistics for the 167 women who were abstinent for at least 1 month and who comprised the analysis sample for objectives III and IV. One hundred twenty-six (75.4%) women were classified as "highly adherent" (ie, used ≥7 days' patches) and had used patches for a mean of 20.5 (*SD* 5.7) days. Forty-one (24.6%) women had lower adherence (≤6 days) and used patches for a mean of 3.6 (*SD* 2.0) days. At delivery, 126 (75.4%) women were classified as highly adherent and reported using patches on average for 31.5 (*SD* 16.4) days and 41 (24.6%) were less adherent women who reported using patches for an average of 3.6 (*SD* 2.0) days. A likelihood ratio test was used to test whether adherence decreased in a nonlinear fashion. These tests suggested that adherence decreased in a linear fashion at 1 month follow-up (P = .121) and at delivery (P = .999). Therefore, adherence was included as a continuous variable in the subsequent analyses.

Investigation of Relationship Between Women's Characteristics and Adherence to Trial Patches (Objective I)

Factors associated with adherence at 1 month and delivery are detailed in Table 3 and Table 4. At 1 month, univariable analyses showed that women with higher HSI scores and higher baseline cotinine level had lower odds of adherence, whilst women assigned to NRT and who had remained in full-time education beyond the age of 16 years had higher odds of adherence. In a multivariable analysis, only the inverse association with baseline cotinine (adjusted β −0.08, 95% confidence interval [CI] −0.15 to −0.01, P = .020) and treatment assignment to NRT (adjusted β 2.59, 95% CI 1.50 to 3.68, P < .001) remained significant (Table 3).

At delivery, univariable analyses showed that treatment assignment to NRT and age when full-time education was completed were associated with increased odds of adherence. A higher HSI score was also found to be inversely associated with the odds of adherence. A multivariable analysis of these factors found that HSI's inverse association (adjusted β −0.27, 95% CI −0.50 to −0.05, $P < .001$) and treatment assignment to NRT (adjusted β 0.51, 95% CI 0.29 to 0.72, $P < .001$) remained significant (Table 4).

Investigation of Relationship Between Adherence and Cessation and Whether Potential Confounding Explains This (Objective II)

After adjustment for baseline characteristics, at 1 month, for each extra day's use of trial patches (ie, placebo or nicotine-containing), the odds of cessation at 1 month increased by 11% (adjusted odds ratio [*OR*] 1.11, 95% CI 1.08 to 1.13, $P < .001$; Table 5). After adjustment for baseline characteristics, at delivery, the odds of cessation increased by 6% (adjusted *OR* 1.06, 95% CI 1.03 to 1.09, $P < .001$) for each extra day trial patches were used (Table 6).

Investigation of Reverse Causation as an Explanation for Adherence-Cessation Association (Objective III)

Within the 167 women who were abstinent from quit date until 1 month, there was no statistically significant difference in the odds of cessation at delivery between women who were highly adherent and those who had "lower adherence" (*OR*: 0.63, 95% CI: 0.31 to 1.27, $P = .196$).

Investigation of Whether a Treatment Assignment-Adherence Interaction Exists for Smoking Cessation (Objective IV)

In the full sample of pregnant smokers ($n = 957$), the likelihood ratio test indicated that there was evidence of an interaction between adherence and treatment assignment, and the odds of smoking cessation at delivery ($P = .002$). Amongst the women who used placebo patches, there was no significant increase in the odds of cessation at delivery in those who were highly adherent compared to those who had lower adherence (*OR* 0.94, 95% CI 0.47 to 1.88, $P = .858$). However, amongst the women who used NRT patches, there was a significant increase in the odds of cessation at

Table 1. Baseline Participant Characteristics of the Main Study Group ($n = 957$)

	Adherence[a]				
	Low		High		
Variable	Placebo ($n = 289$)	NRT ($n = 235$)	Placebo ($n = 194$)	NRT ($n = 239$)	Overall ($n = 957$)
Age (y) [median (IQR)]	24.8 (21.2–30.7)	24.8 (21.5–28.7)	25.9 (21.7–30.9)	25.6 (21.4–31.0)	25.1 (21.5–30.7)
Primiparous	36.3%	35.2%	35.7%	39.9%	36.9%
Age full-time education finished					
≤16	77.6%	79.6%	79.0%	77.9%	78.4%
>16	22.4%	20.4%	21.0%	22.1%	21.5%
Ethnicity					
British–white	96.5%	96.8%	98.7%	96.9%	97.2%
Other	3.5%	3.2%	1.3%	3.1%	2.8%
Gestational age (wk) [median (IQR)]	15.6 (13.7–18.7)	15.0 (13.4–18.1)	14.9 (13.4–18.0)	15.0 (13.3–18.3)	15.1 (13.4–18.3)
Baseline cotinine (ng/ml) [median (IQR)]	124.0 (74.5–180.8)	123.8 (87.1–178.4)	114.4 (79.6–167.6)	118.5 (73.5–179.8)	121.2 (78.1–176.1)
Cigarettes currently smoked [mean (*SD*)]	14.0 (6.1)	15.2 (7.6)	13.5 (6.3)	13.0 (5.9)	13.9 (6.6)

IQR = interquartile range; NRT = nicotine replacement therapy.
[a]High adherence based on median split of adherence at 1-month follow-up.

Table 2. Baseline Participant Characteristics of the Restricted Study Group ($n = 167$)

	Adherence[a]				
	Low		High		
Variable	Placebo ($n = 24$)	NRT ($n = 17$)	Placebo ($n = 35$)	NRT ($n = 91$)	Overall ($n = 167$)
Age (y) [median (IQR)]	27.6 (16.7–43.3)	24.6 (18.5–40.0)	26.3 (17.8–39.8)	27.4 (16.8–41.1)	25.7 (21.9–32.0)
Primiparous	50.0%	23.5%	40.0%	35.2%	37.1%
Age full-time education finished					
≤16	62.5%	76.5%	74.3%	67.0%	68.9%
>16	37.5%	23.5%	25.7%	33.0%	31.1%
Ethnicity					
British–white	95.8%	100.0%	94.3%	96.7%	96.4%
Other	4.2%	0.0%	5.7%	3.3%	3.6%
Gestational age (wk) [median (IQR)]	16.7 (14.6–20.7)	14.0 (12.7–15.9)	14.4 (13.1–17.0)	14.9 (13.3–19.0)	15.0 (13.3–18.6)
Baseline cotinine (ng/ml) [median (IQR)]	75.0 (58.9–130.0)	68.3 (45.4–116.3)	80.2 (39.2–124.8)	99.9 (62.0–163.2)	91.2 (57.5–137.7)
Cigarettes currently smoked [mean (*SD*)]	12.8 (6.6)	13.1 (7.8)	10.0 (5.4)	12.8 (6.4)	12.2 (6.5)

IQR = interquartile range; NRT = nicotine replacement therapy.
[a]High adherence based on median split of adherence at 1-month follow-up.

Table 3. Univariable and Multivariable Associations With Adherence Reported at 1 Month

		Crude	95% CI			Adjusted	95% CI		LRT
Variable	*N*	β	Lower	Upper	*P*	β	Lower	Upper	*P*
Age (y)	957	0.07	−0.02	0.16	.144	—	—	—	—
Ethnicity									
Other	27	−1.65	−5.00	1.70	.333	—	—	—	—
British–white	930	ref	—	—		—	—	—	
Age full-time education finished									
≤16	751	ref	—	—	.044	—	—	—	—
>16	206	1.38	0.03	2.73		—	—	—	
Heaviness of smoking index (HSI)									
0–3	631	ref	—	—	.033	—	—	—	—
4–6	326	−1.27	−2.44	−0.11		—	—	—	
Partners' smoking status									
Nonsmoking	225	ref	—	—	.627	—	—	—	—
Smoking	654	0.25	−1.08	1.57		—	—	—	
Not applicable	78	1.11	−1.15	3.36		—	—	—	
Parity									
≤1	649	ref	—	—	.933	—	—	—	—
2 or 3	256	−0.19	−1.46	1.08		—	—	—	
≥4	52	−0.34	−2.81	2.14		—	—	—	
Baseline cotinine (ng × 10^{-1}/ml)									
12.1 (7.8–17.6), median (IQR)	957	−0.08	−0.15	−0.01	.021	−0.08	−0.15	−0.01	.020
BMI									
<18.5	28	1.43	−1.93	4.79	.324	—	—	—	—
18.5–24.9	362	ref	—	—		—	—	—	
25–29.9	267	1.17	−0.22	2.55		—	—	—	
>30	254	0.60	−0.80	2.00		—	—	—	
Missing	46	2.23	−0.45	4.91		—	—	—	
Length of first behavioral support session									
16–30	143	ref	—	—	.585	—	—	—	—
31–45	791	−0.06	−1.61	1.50		—	—	—	
>60	23	−1.95	−5.81	1.90		—	—	—	
Previous preterm births									
0	872	ref	—	—	.608	—	—	—	—
≥1	85	0.51	−1.44	2.46		—	—	—	
Previous use of NRT									
No	914	ref	—	—	.136	—	—	—	—
Yes	43	2.03	−0.64	4.71		—	—	—	
Gestational age (wk)									
12–19	766	ref	—	—	.572	—	—	—	—
20–24	191	−0.40	−1.78	0.99		—	—	—	
Treatment assignment									
Placebo	483	ref	—	—	<.001	ref	—	—	<.001
NRT	474	2.67	1.58	3.77		2.59	1.50	3.68	

BMI = body mass index; CI = confidence interval; IQR = interquartile range; LRT = likelihood ratio test; NRT = nicotine replacement therapy.

delivery in those who were highly adherent compared to those who had lower adherence (*OR* 2.47, 95% CI 1.32 to 4.63, *P* = .004).

In the sensitivity analysis restricted to a subgroup of women who were abstinent at 1 month postquit date (*N* = 167), the likelihood ratio test found no evidence of an interaction between adherence to treatment and treatment assignment on the odds of cessation at delivery (*P* = .151).

Discussion

Main Findings

In this trial, women allocated to active NRT patches had greater adherence than women allocated to placebo patches and pregnant smokers who were more dependent used patches for fewer days than less dependent women. After adjusting for confounding, we found a strong positive relationship between adherence to treatment and cessation. This association was modified by whether the patch contained NRT; there was no evidence that greater use of placebo patch was associated with cessation but there was a strong association with active patch. We could not exclude reverse causation as an explanation for either the overall adherence-cessation relationship or its moderation by the content of transdermal patches.

Strengths and Limitations

Strengths of this study include its novelty, size and the rigor of data collection, and of analysis techniques employed; it is only the second study to investigate adherence to NRT in pregnant quitters, but is almost 10 times larger than the earlier study[11] and is the first to employ multivariable methods to adjust for confounding. As such

Table 4. Univariable and Multivariable Associations With Adherence Reported at Delivery

		Crude	95% CI			Adjusted	95% CI		LRT
Variable	*N*	β[a]	Lower	Upper	*P*	β[a]	Lower	Upper	*P*
Age (y)	957	0.01	−0.01	0.03	.154	—	—	—	—
Ethnicity									
Other	27	−0.41	−1.07	0.25	.224	—	—	—	—
British–white	930	ref	—	—		—	—	—	
Age full-time education finished									
≤16	751	ref	—	—	.048	—	—	—	—
>16	206	0.27	0.00	0.53		—	—	—	
Heaviness of smoking index (HSI)									
0–3	631	ref	—	—	.026	ref	—	—	<.001
4–6	326	−0.26	−0.49	−0.03		−0.27	−0.50	−0.05	
Partners' smoking status									
Nonsmoking	225	ref	—	—	.811	—	—	—	—
Smoking	654	0.08	−0.18	0.34		—	—	—	
Not applicable	78	0.11	−0.34	0.55		—	—	—	
Parity									
≤1	649	ref	—	—	.654	—	—	—	—
2 or 3	256	−0.08	−0.33	0.17		—	—	—	
≥4	52	0.14	−0.34	0.63		—	—	—	
Baseline cotinine (ng × 10^{-1}/ml)									
12.1 (7.8–17.6), median (IQR)	957	−0.01	−0.03	0.00	.053	—	—	—	—
BMI									
<18.5	28	0.10	−0.56	0.77	.228	—	—	—	—
18.5–24.9	362	ref	—	—		—	—	—	
25–29.9	267	0.32	0.05	0.60		—	—	—	
>30	254	0.10	−0.18	0.37		—	—	—	
Missing	46	0.22	−0.31	0.75		—	—	—	
Length of first behavioral support session									
16–30	143	ref	—	—	.471	—	—	—	—
31–45	791	0.06	−0.25	0.36		—	—	—	
>60	23	−0.38	−1.14	0.38		—	—	—	
Previous preterm births									
0	872	ref	—	—	.496	—	—	—	—
≥1	85	0.13	−0.25	0.52		—	—	—	
Previous use of NRT									
No	914	ref	—	—	.282	—	—	—	—
Yes	43	0.29	−0.24	0.82		—	—	—	
Gestational age (wk)									
12–19	766	ref	—	—	.963	—	—	—	—
20–24	191	0.01	−0.27	0.28		—	—	—	
Treatment assignment									
Placebo	483	ref	—	—	<.001	ref	—	—	<.001
NRT	474	0.50	0.29	0.72		0.51	0.29	0.72	

BMI = body mass index; CI = confidence interval; LRT = likelihood ratio test; NRT = nicotine replacement therapy.
[a]β value and regression coefficients using square root transformed adherence.

it adds substantially to the evidence base on adherence to NRT in pregnancy. Other strengths are that data were obtained as part of a well-conducted randomized controlled trial with validated smoking and adherence data available at two time points having been obtained by specially-trained research midwives.

One limitation of this analysis is that adherence was self-reported so women may have over or under-estimated use of treatment. Women who failed to achieve abstinence might have felt pressure to over-report use of patches; however, this would be expected to weaken the observed association between adherence and cessation and thus this is unlikely to create a spurious association between the two. Furthermore, retrospective self-reported adherence does not allow us to investigate women's day to day pattern of NRT use, which might provide further detail into when might be most effective for pregnant women to use NRT for smoking cessation. Future studies should aim to record this through use of daily diaries or through use of electronic form or App. Another limitation is that some motivational factors that have previously been found to predict treatment success[14] were not collected in the SNAP trial. As it was not possible to adjust for variables which had not been collected, residual confounding by nonmeasured motivational factors could explain the relationship between adherence and cessation. For example, stronger motivation to quit might result in women smoking less and more motivated women might also be expected to adhere better to patch treatment, explaining the relationship between adherence and lower levels of nicotine addiction. Other factors include the level of social

Table 5. Multivariable Associations With Validated Cessation at 1 Month (*n* = 957, 91.1%)

Variable	*N*	Adjusted *OR*	95% CI		LRT
			Lower	Upper	*P*
Adherence 0–28 days	957	1.11	1.09	1.13	<.001
Age full-time education finished					
≤16	751	ref	—	—	.044
>16	206	1.54	1.01	2.35	
Heaviness of smoking index (HSI)					
0–3	631	ref	—	—	.001
4–6	326	0.75	0.63	0.88	
Baseline cotinine (ng × 10^{-1}/ml)	957	0.94	0.91	0.97	<.001
Treatment assignment					
Placebo	483	ref	—	—	.004
NRT	474	1.77	1.20	2.61	

CI = confidence interval; LRT = likelihood ratio test; NRT = nicotine replacement therapy; *OR* = odds ratio.

Table 6. Multivariable Associations With Validated Cessation at Delivery (*n* = 957, 91.1%)

Variable	*N*	Adjusted	95% Confidence Interval		LRT
		OR	Lower	Upper	*P*
Adherence 0–56 days	957	1.06	1.03	1.09	<.001
Heaviness of smoking index (HSI)					
0–3	631	ref	—	—	.002
4–6	326	0.74	0.61	0.89	
Treatment assignment					
Placebo	483	ref	—	—	.355
NRT	474	1.25	0.78	2.00	

LRT = likelihood ratio test; NRT = nicotine replacement therapy; *OR* = odds ratio.

support received from other family members in quitting or whether women experienced stress during pregnancy, both of which could influence adherence to NRT and have been found to be associated with cessation; future studies should attempt to collect these variables to limit residual confounding.[14] However, this alone would not fully explain the better outcomes seen amongst women with stronger adherence to nicotine patches. A further limitation is that only 167 women were abstinent at 1 month; hence, sensitivity analyses within this subgroup, which investigated the adherence-cessation relationship and its moderation, may be underpowered. Consequently, not finding a positive association between treatment adherence (ie, placebo or nicotine) and cessation in this subgroup could either be because reverse causality explains this relationship within the larger group or because there is insufficient power in the restricted subgroup to detect such an association. This may be particularly important as, using these analysis methods, the strength of any association between adherence early in a quit attempt and much later relapse, is assessing only adherence around the time of a potential relapse. The analysis, therefore, relies on the assumption that early adherence is associated with later adherence and the degree to which these two are imperfectly correlated will also undermine the apparent strength of the association between adherence and relapse.

Findings in the Context of Previous Work

Adherence to medications in pregnancy generally is low[15] and very little is known about adherence to NRT in pregnancy; findings from the only previous study are summarized in the introduction. However, adherence to NRT by nonpregnant smokers does seem important for achieving smoking cessation. A systematic review investigating the relationship between adherence to smoking cessation pharmacotherapy and cessation in nonpregnant smokers concluded that "lack of adherence to NRT regimens undermines effectiveness in clinical studies."[7] This review only considered studies in which analytic strategies employed meant that reverse causation could not explain any demonstrated adherence-cessation relationships; only four studies meeting this criterion were identified and all involved NRT. Two studies were underpowered, but the remaining adequately-powered ones showed that in the absence of potential reverse causation, adherence to NRT resulted in higher cessation rates.

Findings from analyses presented in this paper require careful interpretation. There are three possible explanations of the association between adherence and cessation. The first is reverse causation; women who fail in a quit attempt stop using patches, as instructed, and thus failure to achieve abstinence causes low adherence. This is supported by our finding that higher dependence, known to be associated with early relapse,[16] was associated with lower adherence. Studies that do not take reverse causation into account may overestimate the strength of association between adherence and cessation; this is the first study that takes account of reverse causation in an investigation of the association between adherence and cessation in pregnancy. Nevertheless, this may not be the complete explanation of the association because, even controlling for markers of dependence, we observed an association between adherence and cessation. The second is that a person who follows behavioral advice and adheres to medication is also more prone to follow other behavioral advice and show greater self-control and therefore more likely to achieve cessation, independently of any benefit of medication. This explanation is not supported by our data, however.

Women allocated to placebo who adhered to their treatment regimen were not more likely to achieve cessation than women who did not adhere well, whereas women allocated to nicotine patches were. This supports the third explanation, which is that higher adherence to nicotine-containing patches prevents relapse. Unfortunately, our analyses in the "restricted" sample in which reverse causation was not possible did not provide further evidence for this explanation. Taken together, though, the data do indicate that poor adherence to NRT may be a particular problem in pregnancy and suggest that future trials of NRT in pregnancy may need to pay particular attention to the behavioral components to support greater adherence to medication.

Conclusions

Adherence to treatment was associated with smoking cessation but it is not clear if this was due to active NRT treatment being effective, reverse causation or if the propensity to adhere to treatment was indicative of (unmeasured) women's characteristics which made them more likely to achieve abstinence anyway. As a key influence on adherence was the provision of nicotine and at similar adherence levels, NRT patches were associated with greater odds of cessation than placebo ones, a likely hypothesis is that NRT patches, if used sufficiently, may be effective for smoking cessation in pregnancy.

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